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Primary Dermal Irritation Potential of JA-2 Solid Propellant in Rabbits

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MAMMALIAN TOXICOLOGY BRANCH
DIVISION OF TOXICOLOGY

October 1989

Toxicology Series: 175

LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

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Donald G. Corby 30 Oct 89

Donald G. Corby (date)
COL, MC
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The primary dermal irritation potential of JA-2 Solid Propellant was determined in female New Zealand White rabbits by using a modified Draize method. Very slight erythema and edema were observed in 1 of 8 rabbits one hour after dosing. This rabbit had returned to normal by 24 hours after dosing. No other recognizable skin reaction was detected at any time during the 14-day observation period. The test compound was non-irritating under conditions of this study. (Dermal toxicity)

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ABSTRACT

The primary dermal irritation potential of JA-2 Solid Propellant was determined in female New Zealand White rabbits by using a modified Draize method. Very slight erythema and edema were observed in 1 of 8 rabbits one hour after dosing. This rabbit had returned to normal by 24 hours after dosing. No other recognizable skin reaction was detected at any time during the 14-day observation period. The test compound was non-irritating under conditions of this study.

KEY WORDS: Primary Dermal Irritation, JA-2 Solid Propellant, Mammalian Toxicology, Rabbit, Munition, Nitroglycerin, Diethyleneglycol dinitrate

PREFACE

TYPE REPORT: Primary Dermal Irritation GLP Study Report

TESTING FACILITY:

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SPONSOR:

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Project Officer: Gunda Reddy, PhD

PROJECT/WORK UNIT/APC: 3E162720A835/180/TLB0

GLP STUDY NUMBER: 85019

STUDY DIRECTOR: LTC Don W. Korte, Jr., PhD, MSC
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CO-INVESTIGATOR: SSG James D. Justus, MPA, USA

PATHOLOGIST: MAJ G. Tracey Makovec, DVM, VC, Diplomate,
American College of Veterinary Pathologists

REPORT AND DATA MANAGEMENT:

A copy of the final report, study protocol, retired SOPs, raw data, analytical, stability, and purity data of the test compound, and an aliquot of the test compound will be retained in the LAIR Archives.

TEST SUBSTANCE: JA-2 Solid Propellant

INCLUSIVE STUDY DATES: 14 November - 17 December 1985

OBJECTIVE: The objective of this study was to determine the primary dermal irritation potential of JA-2 Solid Propellant in female New Zealand White rabbits.

ACKNOWLEDGMENTS

SP4 James J. Fischer, SP4 Scott L. Schwebe, and SP4 Theresa L. Polk provided technical assistance; SP4 Paul B. Simboli provided assistance for the chemical analysis; Diane Arevelo and Obie Goodrich provided care for the animals; and Colleen S. Kamiyama provided secretarial assistance.

SIGNATURES OF PRINCIPAL SCIENTISTS INVOLVED IN THE STUDY

We, the undersigned, declare that GLP Study 85019 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

Don W. Korte, Jr 30 Oct 89

DON W. KORTE JR., PhD / DATE
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Study Director

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EARL W. MORGAN, DVM / DATE
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ATTENTION OF:

SGRD-ULZ-QA 26 October 1989

MEMORANDUM FOR RECORD

SUBJECT: GLP Compliance for GLP Study 85Ø19

1. This is to certify that the protocol for LAIR GLP Study 85Ø19 was reviewed on 1Ø May 1985.

2. The institute report entitled "Primary Dermal Irritation Potential of JA-2 Solid Propellant in Rabbits," Toxicology Series 175, was audited on 25 October 1989.

Carolyn M. Lewis

CAROLYN M. LEWIS
Diplomate, American Board of
Toxicology
Quality Assurance Auditor

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Primary Dermal Irritation Potential of JA-2 Solid Propellant in Rabbits– Morgan *et al.*

INTRODUCTION

The Department of Defense is considering the use of diethyleneglycol dinitrate (DEGDN), triethyleneglycol dinitrate (TEGDN), or trimethylolethane trinitrate (TMETN) as a replacement for nitroglycerin in new propellant formulations. However, considerable gaps in the toxicology data of the compounds were identified during a review of their health effects (1) conducted for the US Army Biomedical Research and Development Laboratory (USABRDL). Consequently, USABRDL has tasked the Division of Toxicology, Letterman Army Institute of Research (LAIR), to conduct an initial health effects evaluation of the proposed replacement nitrate esters. This initial evaluation of DEGDN, TMETN, TEGDN, and two DEGDN-based propellants, JA-2 and DIGL-RP, includes the Ames mutagenicity assay, acute oral toxicity tests in rats and mice, acute dermal toxicity in rabbits, dermal and ocular irritation studies in rabbits, and dermal sensitization studies in guinea pigs.

Objective of Study

The objective of this study was to determine the primary dermal irritation potential of JA-2 Solid Propellant in female New Zealand White rabbits.

MATERIALS

Test Substance

Chemical Name: JA-2 Solid Propellant

LAIR Code Number: TP56

Description: Solid black cylinders (stick configuration)

Lot Number: RAD83K001S153

JA-2 Solid Propellant was received in the stick configuration. It was ground into a fine powder for the study (Appendix A). Other test substance information is presented in Appendix A.

Animal Data

Eight female New Zealand White rabbits (Elkhorn Rabbitry, Watsonville, CA), identified individually with ear tattooes numbered 85F301 to 85F308 inclusive, were assigned to the study. The animal weights on dosing day (3 Dec 85) ranged from 2.5 to 3.0 kg. Additional animal data appear in Appendix B.

Husbandry

The rabbits were housed individually in stainless steel, screen-bottomed, battery-type cages with automatically flushing dump tanks. The diet consisted of 150 g per day of Certified Purina Chow® Diet 5322 (Ralston Purina Company, Checkerboard Square, St. Louis, MO); water was provided by continuous drip from a central line. The animal room temperature was maintained at 17.0° to 19.5°C with a relative humidity range of 50 to 65 percent with short spikes up to 78 percent associated with room cleaning. The photoperiod was 12 hours of light per day.

METHODS

Group Assignment/Acclimation

Study animals were acclimated for 6 days to the study room following a 14-day quarantine by the Division of Animal Care and Services. During this period they were observed daily for signs of illness. They were treated prophylactically for ear mites with a single dose of Canex® and mineral oil instilled in the ears.

Test Procedures

This study was conducted in accordance with EPA guidelines (2) and LAIR SOP-OP-STX-34 (3).

The backs of 8 rabbits were close-clipped 24 hours before the actual dosing. The clipped area was divided into 4 quadrants designated HV (4, 5). Site I was a sham patch control site. Sites II and III were test compound sites. Site IV was treated with an isotonic saline control patch. A standard dose of 0.5 g of powdered JA-2 was mixed with 0.5 ml isotonic saline (Viaflex®, Sodium Chloride Injection, USP; Travenol Laboratories, Inc., Deerfield, IL) to make a paste which was then placed on 1-inch (2.5 cm) square gauze patches that were taped to the appropriate sites. Blenderm® (Medical Products Division of 3M, Saint Paul, MN), a semi- impervious, hypoallergenic surgical tape, was used to hold the patches in place. Vet Wrap® (Animal Care Products Division of 3M, Saint Paul, MN) was then wrapped securely around the animal. The test compound was left in contact with the skin for 4 hours. At the end of the exposure period the wrapping and patches were removed, and the areas were scored one hour later.

Observations

The grading and scoring for dermal reactions were performed according to Table 1. Scoring and grading were performed at approximately 1, 24, 48, and 72 hours, and 7 and 14 days after removal of the patch. Observations for clinical signs were made daily from 3 to 17 December 1985. After 14 days the animals were submitted for necropsy.

Duration of Study

Appendix C is a complete historical listing of study events.

Changes/Deviations

Ventilation fans in the building were turned off for several hours on 7 Dec 85. This resulted in a temperature and humidity increase in the animal room. The temperature rose to 20°C and the humidity rose to 79% for a

TABLE 1 (4)
Evaluation of Skin Reactions

Erythema and Eschar Formation		
No erythema	0	
Very slight erythema (barely perceptible)	1	
Well-defined erythema	2	
Moderate-to-severe erythema	3	
Severe erythema (beet-redness to slight eschar formation [injurious in depth])	4	
Possible total erythema score		4
Edema Formation		
No edema	0	
Very slight edema (barely perceptible)	1	
Slight edema (edges of area well-defined by definite raising)	2	
Moderate edema (edges raised approximately 1 mm)	3	
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4	
Possible total edema score		4
Possible total score for primary irritation		8

period of approximately four hours. This is not believed to have had any effect on the study.

Storage of Raw Data and Final Report

A copy of the final report, study protocols, raw data, retired SOPs, and an aliquot of the test compound were retained in the LAIR Archives.

RESULTS

Animals were scored for erythema and edema at each patch site. Rabbit 85F307 was observed to have very slight erythema and edema one hour after dosing at both test compound sites. The skin at the sham patch site on animal 85F301 had slight erythema at one hour after patch removal. Both animals returned to normal by 24 hours after dosing and remained normal throughout the study. No other recognizable skin reaction was detected at any time during the 14-day observation period. The vehicle control patch sites were normal throughout the study. Total scores (erythema plus edema) for the dermal irritation potential in each rabbit were tabulated (Appendix D). Fourteen days after topical application there were no gross lesions that could be attributed to exposure to the test material (Appendix E).

DISCUSSION

The modified Draize dermal irritation test as performed for this study has proven reliable for detecting non-irritating substances and severe irritants but considerably less reliable for detecting mild and moderate irritants (5). Consequently, many systems have been used to score and categorize the dermal irritation potential of a test compound. The system used by the Toxicity Testing Program at LAIR is an adaptation of one used at the U.S. Army Environmental Hygiene Agency (6). It develops a dermal irritation index based on the peak net mean score, which is the maximum net mean score calculated during the 72-hour observation period. Non-irritating compounds have peak net mean scores of 0.0 to 0.5. Mild irritants have peak net mean

scores of 0.51 to 2.0. Moderate irritants have peak net mean scores of 2.1 to 5.0. Severe irritants have peak net mean scores of 5.1 to 8.0. JA-2 Solid Propellant produced very slight erythema and edema in 1 of 8 rabbits. The peak net mean score for the test compound was 0.0; therefore, JA-2 was classified as a non-irritant.

CONCLUSION

The test compound, JA-2 Solid Propellant, is not a dermal irritant under conditions of this assay.

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1. Holleman JW, Ross RH, Carroll JW. Problem definition study on the health effects of diethyleneglycol dinitrate, triethyleneglycol dinitrate, and trimethylolethane trinitrate and their respective combustion products. Frederick, MD: US Army Medical Bioengineering Research and Development Laboratory, 1983, DTIC No. ADA 127846.

2. Environmental Protection Agency. Office of Pesticide and Toxic Substances, Office of Toxic Substances (TS-792). Primary dermal irritation. In: Health effects test guidelines. Washington, DC: Environmental Protection Agency, August 1982; EPA 560/6-82-001.

3. Primary dermal irritation study. LAIR Standard Operating Procedure OP-STX-34, Presidio of San Francisco, CA: Letterman Army Institute of Research, 1 August 1984.

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5. McCreesh AH, Steinberg M. Skin irritation testing in animals. In: Marzulli FN, Maibach HI, eds. Dermatotoxicology. 3rd ed. Washington, DC: Hemisphere Publishing Corp, 1987: 153-172.

6. US Army Environmental Hygiene Agency. Topical hazard evaluation program. Procedural guide. Aberdeen Proving Ground, MD: US Army Environmental Hygiene Agency, October 1985.

Appendix A: CHEMICAL DATA

Test substance: JA-2 Solid Propellant

LAIR Code Number: TP56

Physical State: Solid black cylinders (stick configuration)

Preparation of test substance for dosing: The cylinders of JA-2 were ground to a fine powder under liquid nitrogen using a Spex freezer mill. The powder was then sieved through an 80-mesh screen.

Chemical Analysis:

DEGDN was the only major component of JA-2 which could be easily analyzed.[1] To determine the percent DEGDN in the JA-2 propellant, samples of JA-2 powder were added to individual 100 ml volumetric flasks. After dilution to volume with 95% ethanol, a second 1:100 dilution was performed. These solutions were analyzed by HPLC. Standards consisted of solutions of DEGDN in ethanol ranging in concentration from 164.5 to 670.5 µg/ml. Analysis of DEGDN by HPLC was performed under the following conditions: column, Brownlee RP-18 (4.6 x 250 mm, Brownlee Labs, Inc., Santa Clara, CA): solvent system, 40% water - 60% acetonitrile); flow rate, 0.9 ml/min; wavelength monitored, 210 nm.[2] Under these conditions, DEGDN eluted with a retention time of approximately 5.4 min.

The results from the analysis of standards and JA-2 powder samples are presented in Tables 1 and 2.

Table 1. Analysis of standards

Concentration of Standard (µg/ml)	Peak Area* (x 10^{-7})
164.5	0.94
191.0	1.09
275.5	1.60
299.4	1.74
362.0	2.08
399.6	2.31
444.4	2.52
539.8	3.07
585.0	3.32
670.5	3.79

*Average of 2 determinations

Equation for line by linear regression analysis:

$Y = 5.62 \times 10^4 X + 3.51 \times 10^5$, $r^2 = 0.9999$

Appendix A (cont.): CHEMICAL DATA

Table 2. Analysis of JA-2 Powder

Weight of JA-2 Analyzed (mg)	Dilution Factor	Peak Area (x 10-7)	Conc of DEGDN in JA-2 (weight %)*
104.8	100	1.56	25.9
101.6	100	1.57	26.9
109.7	100	1.69	26.8

*Calculated using the equation for the standard curve as follows:
= {[Peak Area - 3.51×10^5]/5.62×10^4} + wgt JA-2 (mg) x 10.

The average value for the concentration of DEGDN in JA-2 was 27% and this agrees closely with the value of 24.82 ± 1.50 % reported in the data sheet provided by the source.

Stability: The aqueous stability of the DEGDN component of JA-2 propellant was determined.[3] The amount of DEGDN in JA-2 suspensions was determined immediately after preparation of a suspension and again 24 hours later. The study was conducted as follows: A suspension of JA-2 in 1% gum tragacanth (200 mg/ml) was prepared. Three 1 ml aliquots were removed from the suspension immediately after preparation and again 24 hours later. The 1 ml samples were transferred to individual 100 ml volumetric flasks. After diluting to volume with ethanol, the solutions were analyzed by HPLC as described above. The average of the peak area values was 2.92 ± 0.12 for the 0 time samples and 2.95 ± 0.11 for the 24-hour samples. These results indicate that there was no decomposition of DEGDN in 1% gum tragacanth for a period of 24 hours.

Source: Radford Army Ammunition Plant, Radford, Virginia
(prime contractor: Hercules Inc, Wilmington, Delaware)

Lot no.: RAD83K001S153

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[1] Wheeler CR. Toxicity Testing of Propellants. Laboratory Notebook #85-12-023, p. 51-61. Letterman Army Institute of Research, Presidio of San Francisco, CA.

[2] Wheeler CW. Nitrocellulose-Nitroguanidine Projects. Laboratory Notebook #84-05-010.3, p. 58. Letterman Army Institute of Research, Presidio of San Francisco, CA.

[3] Wheeler CR. Toxicity Testing of Propellants. Laboratory Notebook #85-12-023, p. 27, 35, 41. Letterman Army Institute of Research, Presidio of San Francisco, CA.

Appendix A (cont.): CHEMICAL DATA

CHEMICAL ANALYSIS FOR JA-2
(Information from the Manufacturer's Data Sheet)

Ingredient	Finished Propellant Percentage
Nitrocellulose (13.8% ±0.05% Nitrogen) (6-12 seconds viscosity)	58.5 ±2.00
Nitroglycerin	15.88 ±1.00
Diethyleneglycol dinitrate (DEGDN)	24.82 ±1.50
Akardit II	0.70 ±0.20
Magnesium Oxide	0.04 Max
Graphite	0.04 Max
Total	100.00%*

*Data provided as listed, Total actually equals 99.98%.

Appendix B: ANIMAL DATA

Species: *Oryctolagus cuniculus*

Strain: New Zealand White (albino)

Source: Elkhorn Rabbitry
5265 Starr Way
Watsonville, CA 95076

Sex: Female

Age: Young adults

Animals in each group: 8 females

Condition of animals at start of study: Normal

Body weight range at dosing: 2.5 to 3.0 kg

Identification procedures: Ear tag, tag numbers
85F301 - 85F308 inclusive.

Pretest conditioning:

1. Quarantine/acclimation from 14 November - 2 December 1985
2. Animal were close-clipped and examined 24 hours before dosing.

Justification: Laboratory rabbits are a proven sensitive animal model for dermal irritation studies.

Appendix C: HISTORICAL LISTING OF STUDY EVENTS

Date	Event
14 Nov 85	Rabbits arrived at LAIR, were examined for illness, and were placed under a 2-week quarantine.
15 Nov 85	Animals were weighed.
18 Nov 85	Animals were tattooed,. All rabbits were treated with Canex® and mineral oil in their ears to prevent ear mites.
14 - 27 Nov 85	Animals were checked daily by Division of Animal Care and Services personnel.
27 Nov 85	Rabbits were removed from quarantine after being certified healthy by a staff veterinarian. The animals were weighed.
27 Nov - 2 Dec 85	Animals were checked daily.
2 Dec 85	Animals were close-clipped and areas marked.
3 Dec 85	Animals were weighed. Test substance was applied for 4 hours. Patches were removed and sites were scored after one hour.
3 - 17 Dec 85	Animals were observed daily.
3 - 6 Dec 85	Areas were scored at 1, 24, 48, and 72 hours after patch removal.
10 Dec 85	Animals were weighed and scored.
17 Dec 85	Animals were weighed, scored and submitted to necropsy.

Appendix D: DERMAL IRRITATION DATA

ANIMAL NUMBER	OBSERVATION	QUADRANT* I	II	III	IV
85F301	30-60 min	1/0†	0/0	0/0	0/0
	24 hr#	0/0	0/0	0/0	0/0
85F302	30-60 min#	0/0	0/0	0/0	0/0
85F303	30-60 min#	0/0	0/0	0/0	0/0
85F304	30-60 min#	0/0	0/0	0/0	0/0
85F305	30-60 min#	0/0	0/0	0/0	0/0
85F306	30-60 min#	0/0	0/0	0/0	0/0
85F307	30-60 min	0/0	1/1	1/1	0/0
	24 hr#	0/0	0/0	0/0	0/0
85F308	30-60 min#	0/0	0/0	0/0	0/0

* Quadrant I = sham; II, III = treated; IV = saline

† Scores are displayed as erythema/edema

\# Scores were 0/0 in all quadrants for remaining observations

Appendix D (cont.): DERMAL IRRITATION DATA

(Test/Sham/Vehicle)

ANIMAL NUMBER	30-60 Min	24 h	48 h	72 h*
85F301	0/1/0	0/0/0	0/0/0	0/0/0
85F302	0/0/0	0/0/0	0/0/0	0/0/0
85F303	0/0/0	0/0/0	0/0/0	0/0/0
85F304	0/0/0	0/0/0	0/0/0	0/0/0
85F305	0/0/0	0/0/0	0/0/0	0/0/0
85F306	0/0/0	0/0/0	0/0/0	0/0/0
85F307	1/0/0	0/0/0	0/0/0	0/0/0
85F308	0/0/0	0/0/0	0/0/0	0/0/0
Mean	.125/.125/0	0/0/0	0/0/0	0/0/0
Net Mean Score†	0	0	0	0

* Identical scores were recorded at 7 and 14 days.

† Test Mean - (greater of Vehicle or Sham Mean) = Net Mean Score
The peak net mean score is 0.0; therefore, the Primary Skin Irritation Category is I (**non-irritant**).

Appendix E: PATHOLOGY REPORT

LAIR GLP Study 85019
Dermal Sensitization Study
Primary Investigator: CPT Earl Morgan

Compound: JA2 Propellant/Saline.

Animals: Rabbit/New Zealand White/Females/DOB: 30 August 1985.

Reference: SOP-OP-STX-34.

Procedures:

Euthanasia: Sodium pentobarbital.
Fixative: 10% Neutral buffered formalin.
Histopath: Routine

Gross findings: All animals presented live. Asterick (*) indicates tissue saved for histopathology.

LAIR ACC#	ANIMAL ID#	OBSERVATIONS
38681	85F301	Cecum - pinworms
38682	85F302	Cecum - pinworms
38683	85F303	Cecum - pinworms
38684	85F304	Not remarkable (NR)
38685	85F305	Cecum - pinworms *Lungs - right apical lobe has 1x2cm darkened focus
38686	85F306	Cecum - pinworms
38687	85F307	Cecum - pinworms
38688	85F308	Cecum - pinworms

Microscopic findings:

LAIR ACC#	ANIMAL ID#	MICROSCOPIC DIAGNOSES
38685	85F305	Peribronchitis and perbronchiolitis; lymphocytic, multifocal, mild; with minimal airway ectasis.

Comment: None of the gross or microscopic findings are compound related.

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21 March 1986

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